

Antimicrobial Resistance: The “Ignored” Public Health Care Threat

**Jennifer Thomas, PharmD
Member, Maryland Pharmacy Coalition**

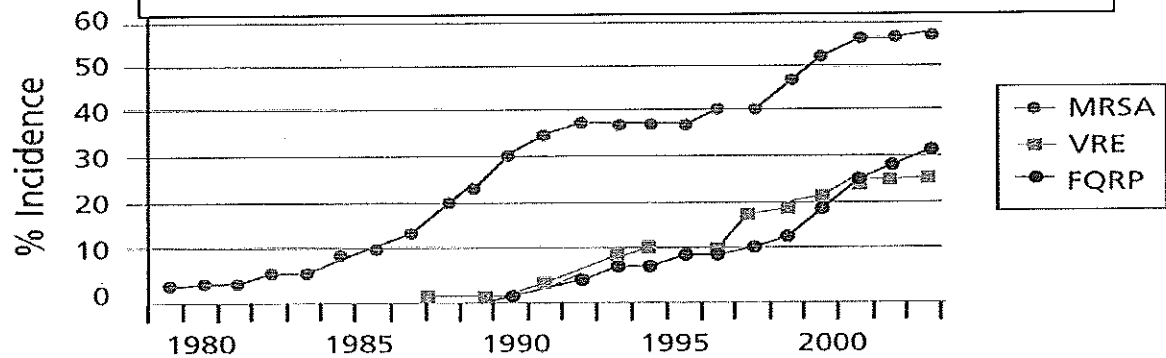
Defining the Problem of Antimicrobial Resistance

Antimicrobial resistance is not a new phenomenon in our society. The experts are stymied about management of antimicrobial resistant cases as indicated by this quote: *“What do you do when you’re faced with an infection, with a very sick patient, and you get a lab report back and every single drug is listed as resistant?” asked Dr. Fred Tenover of the Centers for Disease Control and Prevention (CDC). “This is a major blooming public health crisis.”*

Since the inception of antibiotics, health care providers have been challenged by the issue of antimicrobial resistance. Rapid development of penicillin resistance occurred in the 1940’s shortly after the wide spread use of antibiotics was introduced. Hospital infectious diseases practitioners such as physicians, infection control practitioners, pharmacists, and microbiologists saw a dramatic increase in antimicrobial resistance from the 1940’s to the mid 1980’s primarily in pathogens from respiratory tract infection and otitis media. In the early 1990’s, significant resistance to penicillins and other antimicrobials was noted in *Streptococcus pneumoniae*.² The Active Bacterial Core Surveillance program of the Centers for Disease Control and Prevention (CDC) identified significant increases of penicillin resistance in invasive disease caused by *Streptococcus pneumoniae*. Penicillin resistant isolates were also more likely than susceptible isolates to have multi-drug resistance. The resistance changes continued to proceed with fluoroquinolones. Resistance of up to 40% to 50% to the fluoroquinolones is common for in-patient isolates of many gram-negative pathogens in the *Enterobacteriaceae* family (*E.coli*, *Proteus mirabilis*) and to *Pseudomonas aeruginosa*. In addition, multi-drug resistant carbapenemase and extended spectrum beta-lactamase producing *Klebsiella pneumoniae* and multi-drug resistant *Acinetobacter baumannii* are now resistant to all antimicrobials and exceed our ability to treat these pathogens (personal communication with the Maryland Society of Health Systems Pharmacists, Antimicrobial Stewardship Committee, August 4, 2009). Chart 1 depicts the trends reported by the Centers for Disease Control (CDC) for methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin resistant enterococci (VRE), and fluoroquinolone resistant *Pseudomonas aeruginosa* (FQRP).³ In addition, Figure 1 illustrates the impact of this issue on the segment of our population residing in nursing home facilities.

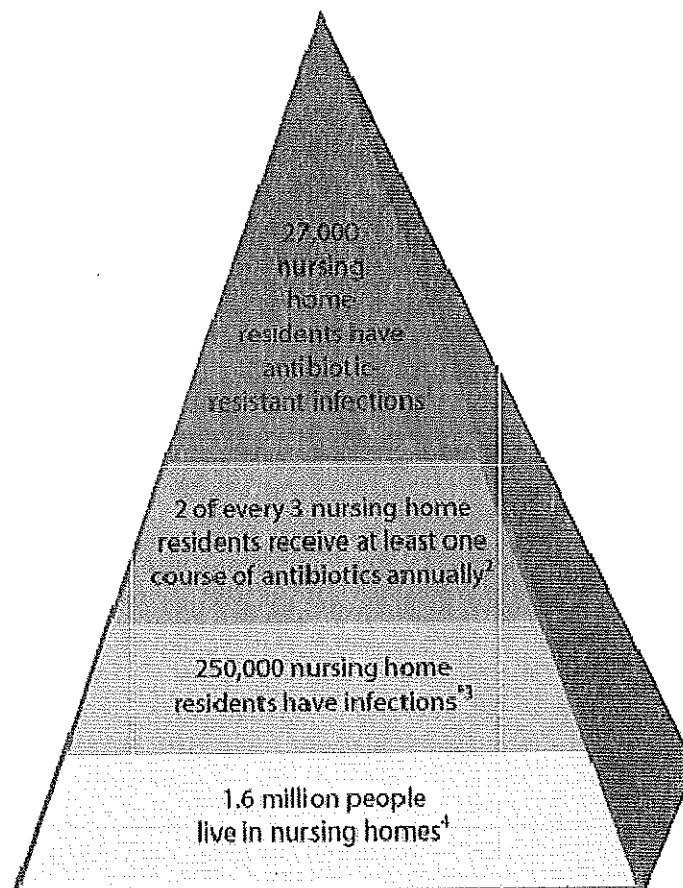
Chart 1: Resistant Strains Spread Rapidly

(Bad Bugs, No Drugs/Strategies to Address Antimicrobial Resistance Act: Our Advocacy Campaign (PPT) 10/24/08 Presentation by Robert J. Guidos, JD



Source: Centers for Disease Control and Prevention

Figure 1: Burden of Infections among U.S. Nursing Home Residents⁴



The estimated costs of infections to the United States (U.S.) public due to antimicrobial resistant organisms is \$4 to \$5 billion dollars annually as reported by the Institute of Medicine report from 1998.⁵ However, the economic impact is difficult to determine and there is the need for research and development of standardized definitions and refined calculations to determine the cost attributable to antimicrobial resistance.^{6,7} The lack of information on the extent of the economic impact may be the reason for the lack of more professional and governmental attention to this matter.⁷ One study estimated the cost for a single infection, *Clostridium difficile* associated-diarrhea, to exceed \$1.1 billion U.S. dollars annually.⁸

While these changes in antimicrobial resistance have occurred over time and the estimated costs due to this public health crisis is estimated to be in the billions of dollars, the general medical community and the general public have not grasped the extent of the problem nor integrated the idea of stewardship with respect to antimicrobial therapy. One explanation is simply a failure to heed the concerns and reports from infectious disease specialists on the subject. It was not until the mid 1990's that professional organizations and governmental committees achieved enough influence in garnering political recognition of the problem. Since 1995, the World Health Organization (WHO), the European Union and the United States (US) have begun implementing plans to address the problem.⁹

Addressing the Problem of Antibiotic Resistance

Developments within the U.S. to address antimicrobial resistance began in earnest in 1999 with the creation of the U.S. Interagency Task Force on Antimicrobial Resistance.¹⁰ This Task Force was charged with developing a national plan to combat antimicrobial resistance. Part of the plan would address and incorporate existing programs such as the National Antimicrobial Resistance Monitoring System (NARMS), established in 1996 by the Food and Drug Administration (FDA) Centers for Veterinary Medicine (FDA CVM), United States Department of Agriculture (USDA), and the Centers for Disease control (CDC) to monitor antimicrobial drug susceptibility changes in select enteric bacterial organisms in humans, animals, and retail meats. The Task Force includes multiple federal agencies and in 2001, the U.S. Agency for International Development joined the Task Force to assist in addressing global antimicrobial resistance issues.¹¹ The Task Force developed a plan, "A Public Health Action Plan to Combat Antimicrobial Resistance" in 2001 which included thirteen items of top priority with a timeline to address each item.¹² The thirteen items were identified under four broad categories: surveillance, prevention and control, research, and product development. Under the category of prevention and control, two of the priority items address the development and execution of educational campaigns as a national health priority. This plan was revised and updated in 2007, is currently being finalized by the Task Force and will be available for public comment in 2009.¹³

The FDA is working with the pharmaceutical industry in drug development and clinical trial design to achieve clear clinical benefit with antimicrobial treatment for a specific infection. The first of these draft guidance document reviews non-inferiority and informative trial designs in community acquired pneumonia (CAP).¹⁴ The Center for Drug Evaluation and Research (CDER) under the FDA, has launched several initiatives to address antimicrobial resistance. One major change to drug-labeling regulations has already been

implemented with directions for prudent and appropriate use and for counseling of patients, particularly regarding the importance of taking antimicrobials as directed.

In 2003, FDA partnered with CDC on its launch of its *Get Smart: Know When Antibiotics Work* campaign.¹⁵ The goal of the campaign is to educate consumers and healthcare professionals on the appropriate use of antibiotics. In the area of food safety, FDA published Guidance for Industry #152 "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern." There are recommendations to drug sponsors on risk assessment approaches for evaluating the likelihood that an antimicrobial drug used to treat a food-producing animal may cause an antimicrobial resistance problem in humans.¹⁶ The FDA also reviews antibiotics for prohibition of use in the animal agriculture industry. This subject is beyond the scope of this article, but supplementing animal feed with antibiotics, termed antibiotic growth promoters (AGP), has been common practice for over 50 years and constitutes more than half of all antimicrobial use worldwide. Development of resistance in animal pathogens and subsequent roles in human infection has been documented. The European Union banned AGPs in 2006, following Denmark's lead that had banned these antibiotics years earlier.^{17, 18} In contrast, the U.S. allows multiple antibiotics to be used in animal agriculture, however secondary to the EU decision there has been more interest on the subject and discussions this year in Congress regarding the use of AGPs in U.S. animal agriculture.¹⁹

The CDC also has another major campaign which focuses on healthcare settings, hospitals and long term care facilities. This campaign may also be remembered as the "12-steps" and includes a tool and fact sheet outlining 12 steps to prevent antimicrobial resistance.²⁰ The campaign promotes four strategies: preventing infection, diagnosing and treating effectively, using antimicrobials wisely, and preventing transmission. The campaign fosters partnerships and implementation of prevention guidelines and use of clinical tools to obtain the project goals.

Fortunately, political awareness of the problems of antimicrobial resistance is increasing. Legislation has been introduced in the last several years named Strategies to Address Antimicrobial Resistance (STAAR) Act, most recently introduced in the 111th Congress by Representative Matheson (D-UT) as H.R. 2400 on May 13, 2009.²¹ The STAAR Act has been endorsed by 25 other professional organizations representing medical doctors, dentists, nursing, public health, infection control and prevention, epidemiology, physical educators, parents and teachers, and pharmacy {American Pharmacists Association (APhA), American Society of Health-System Pharmacists (ASHP), and the Society of Infectious Diseases Pharmacists (SIDP)}. H.R. 2400 would amend the Public Health Service Act to address antimicrobial resistance, by implementing an Antimicrobial Resistance Office, Task Force and Advisory Board. A very important inclusion in the bill is implementation of data systems to report and to capture and measure antimicrobial consumption in humans and animals. Tracking of antimicrobial consumption with surveillance of resistance will aid in the study and supplement research efforts to allow rapid recognition of new problems and to target strategies to manage these events.

Antibiotic Resistance Programs in Maryland

State level awareness of the issues of antimicrobial resistance is reflected in the passage of legislation, SB 286 Antibiotic Resistant Infection Prevention Campaign, during the 2008 legislative session. This bill sponsored by Senator Gladden, subject to the availability and appropriation of funding, directed the development of a public awareness educational campaign on the critical healthcare issue of antibiotic resistant infections. The Maryland Pharmacy Coalition (MPC) supported the legislation and offered the professional support and expertise of pharmacists to collaborate with state and local public health officials in the development and dissemination of educational materials.

A current local and national initiative that is considered a negative campaign and will likely fuel development and selection of resistance is the “free antibiotics” program. As the world encourages the wiser use of antimicrobials, a contradictory message to the public is introduced by the free antibiotics advertisements and coverage by many pharmacy chains and insurance plans. Misconceptions arise due to the medication being “free” and this implies to many that it can be used whenever desired and requested by the patient. The campaign may increase pressure on prescribers to provide an antibiotic when it is not therapeutically necessary. In addition, there is also the concern of stockpiling antibiotics and inappropriate use for seasonal cold and flu and the current novel H1N1 influenza infection. The experts agree this sends the wrong message and is disturbing public health policy. In March 2009, the Infectious Diseases Society of America (IDSA) and the CDC sent joint letters to the supermarket/chain pharmacies to encourage them to join the CDC’s campaign to encourage appropriate use of antimicrobials.²²

Appropriate Antibiotic Use and Stewardship

The concept of appropriate use of antimicrobial therapy as one of stewardship places the responsibility of resistance on many healthcare partners with different motivations: prescribers, patients, providers, industry and the public.⁷ In 2007, guidelines were published that addressed the development of programs to enhance antimicrobial stewardship in institutional settings and provide the outline and metrics to facilitate discussions and inclusion of key individuals, such as administrators, to obtain support (including budgetary) to ensure success of the program.²³ Prior to the publication of these official guidelines, numerous institutions initiated antimicrobial stewardship programs, most managed by the pharmacy department as cost-saving measures. Formal infectious diseases training programs for clinical pharmacists provided the necessary expertise. These programs generally required two years of post-graduate work (residency or fellowship) with one year of concentration in infectious diseases pharmacotherapy.²⁴ Concern over pharmacists providing therapeutic recommendations for antimicrobial therapy was published in a 1997 Infectious Diseases Society of America (IDSA) position statement.²⁵ In general, there has been wide spread acceptance and recognition by the medical community of pharmacist contributions in this area. Clinical Pharmacy Specialists in Infectious Diseases are not qualified to practice medicine, but trained clinical pharmacists working in collaboration with their physician colleagues can make a significant impact on patient care. Pharmacists provide important expertise on dosing requirements incorporating pharmacokinetic and pharmacodynamic principles that may reduce antimicrobial resistance selection and development. Furthermore,

pharmacists have key responsibilities in these programs for documentation, reporting, development of guidelines, education to physicians and other members of the healthcare team, and conducting research on the outcomes of the antimicrobial stewardship programs. A survey conducted in December 2008 by IDSA/SHEA and the Premier Healthcare Alliance on the status of antimicrobial stewardship programs in U.S. hospitals revealed that 48% of hospitals had a program with most of these teams having both pharmacists and physicians involved.²⁶ While the total number of programs may be disappointing, it is much to pharmacists credit and initiative that these programs exist at all.

There are opportunities to expand these programs and the Maryland Society of Health System Pharmacists offers health systems the opportunity to engage in the professional organization, Antimicrobial Stewardship Committee. This committee initiative was led, founded and chaired by Jennifer Thomas, Pharm.D. in 2008. The committee has established relationships with the infection control practitioners of the state through the Maryland Association of Professionals in Infection Control (MD-APIC) and laboratory practitioners within their systems. Members are encouraged to invite and engage infectious diseases physicians in the meetings and discussions. The committee meets monthly, now led by three Co-Chairs, Edina Aydic, Pharm.D (Johns Hopkins Hospital), Jean Lee, Pharm.D. (Sinai Hospital) and Jennifer Thomas, PharmD (Delmarva Foundation). The goal of this committee is to have open discussion, educate and expand our knowledge of community antimicrobial resistance issues as well as to share management strategies and development of guidelines, and antibiograms, and any other tools available on the subject.

As has been noted throughout this article there are many opportunities for pharmacists to utilize their expertise for safe and appropriate antimicrobial use. As one of the most accessible healthcare professionals available to the public, the pharmacist has a responsibility at the point of dispensing, during counseling or obtaining a medication history, or through medication therapy management to share information on antimicrobials and the public health treat of resistance. In the current healthcare reform debate and legislative agenda, pharmacists have an opportunity to share their expertise and voice their opinion. Now is the time to contact your professional organizations and your congressional members to provide your position on addressing the issue of antimicrobial resistance.

References

1. The Brooklyn Antibiotic Resistance Task Force. The Cost of Antibiotic Resistance: Effect of Resistance among *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* on Length of Hospital Stay. *Infect Control Hosp Epidemiol* 2002;23:106-108.
2. Whitney CG, Farley MM, Hadler J, et al. Increasing Prevalence of Multidrug-Resistant *Streptococcus pneumoniae* in the United States. *N Engl J Med* 2000;343:1917-24.
3. Bad Bugs, No Drugs/Strategies to Address Antimicrobial Resistance Act: Our Advocacy Campaign (PPT) 10/24/08 Presentation by Robert J. Guidos, JD, IDSA Director Public Policy & Government Relations before the Society of Infectious Diseases Pharmacists. (<http://www.idsociety.org/STAARAct.htm>, accessed July 13, 2009.
4. Burden of infections among U.S. nursing home residents. <http://www.cdc.gov/drugresistance/healthcare/ltc.htm>, accessed August 13, 2009.
5. Institute of Medicine. Antimicrobial resistance: issues and options. Workshop report. Washington, DC: National Academy Press, 1998
http://books.google.com/books?hl=en&lr=&id=bg68y2z4rh0C&oi=fnd&pg=PA1&dq=Institute+of+Medicine.+Antimicrobial+resistance:+issues+and+options.+Workshop+report.+Washington,+D.C.+National+Academy+Press,+1998&ots=W68xJlkb81&sig=EbvbQ7wPS_h2JuT9DVBZGquDYD_s#v=onepage&q=&f=false, accessed 11 July 2009.
6. Howard D, Cordell R, McGowan JE, et al. Measuring the Economic Costs of Antimicrobial Resistance in Hospital Settings: Summary of the Centers for Disease Control and Prevention–Emory Workshop. *Clin Infect Dis* 2001;33:1573-8.
7. McGowan JE. Economic impact of antimicrobial resistance. *Emerg Infect Dis* 2001;7:286-292.
8. Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. *Clin Infect Dis* 2002;34:346-53.
9. Antimicrobial Resistance: Problem Pathogens and Clinical Countermeasures. Edited by Robert C. Owens and Ebbing Lautenbach. New York: Informa Healthcare, 2008.
10. The Interagency Task Force on Antimicrobial Resistance and *A Public Health Action Plan to Combat Antimicrobial Resistance* http://www.cdc.gov/drugresistance/actionplan/update_08.htm, accessed July 30, 2009.
11. FDA's Role in Antimicrobial Resistance. Subcommittee on Livestock, Dairy and Poultry Committee on Agriculture U.S. House of Representatives <http://www.hhs.gov/asl/testify/2008/09/t20080925a.html>, accessed July 30, 2009.
12. A Public Health Action Plan to Combat Antimicrobial Resistance <http://www.cdc.gov/drugresistance/actionplan/aractionplan.pdf>, accessed July 30, 2009.
13. The Interagency Task Force on Antimicrobial Resistance and A Public Health Action Plan to Combat Antimicrobial Resistance ACTION PLAN UPDATE http://www.cdc.gov/drugresistance/actionplan/update_08.htm, accessed July 30, 2009.
14. Tillotson GS, Echols RM. Clinical Trial Design and Consequences for Drug Development for Community-Acquired Pneumonia: An Industry Perspective. *Clin Infect Dis* 2008;47:S237-S240.
15. Get Smart, Know When Antibiotics Work <http://www.cdc.gov/getsmart/>, accessed July 30, 2009.
16. FDA's Role--Antimicrobial Resistance <http://www.fda.gov/NewsEvents/Testimony/ucm095936.htm>, accessed July 30, 2009.
17. Wegener HC, Aarestrup FM, Jensen LB, et al. Use of Antimicrobial Growth Promoters in Food Animals and Enterococcus faecium Resistance to Therapeutic Antimicrobial Drugs in Europe. *Emerg Infect Dis* 1999;5:329-35.
18. Dibner JJ, Richards JD. Antibiotic Growth Promoters in Agriculture: History and Mode of Action. *Poultry Sciences* 2005;84:634-43.
19. Preservation of Antibiotics For Medical Treatment Act of 2009. <http://www.fda.gov/NewsEvents/Testimony/ucm171715.htm>, accessed July 30, 2009.
20. Campaign to Prevent Antimicrobial Resistance in Healthcare Settings <http://www.cdc.gov/drugresistance/healthcare/patients.htm>, accessed July 30, 2009.
21. IDSA Strategies to Address Antimicrobial Resistance Act <http://www.idsociety.org/STAARAct.htm>, accessed July 13, 2009.
22. IDSA Responds to Supermarkets' Free Antibiotics Promotions <http://news.idsociety.org/idsa/issues/2009-03-01/8.html>, accessed July 30, 2009.

23. Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology (SHEA): Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. Clin Infect Dis 2007;44:159-77.
24. MacDougal C, Polk RE. Antimicrobial Stewardship Programs in Health Care Systems. Clin Micro Rev 2005;18:638-56.
25. Infectious Diseases Society of America. 1997. Hospital pharmacists and infectious diseases specialists. Clin. Infect. Dis. 25:802.
26. IDSA-SHEA-Premier Antimicrobial Stewardship Survey
<http://www.premierinc.com/safety/topics/HAI/downloads/IDSA-SHEA-Adherence-Survey-Results-12102008.pdf>, accessed August 14, 2009.